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November 19, 1999

Dear Sir or Madam:

Attached please find Endotec's response to the draft guidance, ***'Guidance for Industrv and*** **FDA Reviewers *on* Evidence Models for the Least Burdensome Means to Market', September 1, 1999.** We commend you on a splendid effort except for the Alternative global Question # 2 which we find to be most inappropriate.

Sincerely,

John Pappas
Regulatory Affairs

99D-2873

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An Answer to *'Guidance for Industry and FDA Reviewers on* Evidence Models for the Least Burdensome Means to Market', September 1, 1999, On the Appropriateness and Necessity of the Alternative Question # 2

In their conclusion, the authors of the latest draft guidance on the 'least burdensome means' state, 'The challenge of section 205 of FDAMA is to develop an efficient model of medical device development and review that will allow safe and effective products to be developed and marketed to consumers without unnecessary delay and expense to manufacturers. Our goal is to provide a process model for reaching a decision about the need for clinical data and the type of clinical data that are the least burdensome means to support successful premarket review. The agency views this draft guidance as a first step toward developing a useful process model. We encourage our reviewers and other stakeholders to play an active role in refining the model by testing its assumptions."

The following criticisms and proposals are made in this spirit, to refine ". . .the model by testing its assumptions."

It must be stated from the start, that the guidance is a well thought out helpful document, with one major flaw from our standpoint: the alternative question to global question # 2, **"Alternatively one could ask: Is a randomized controlled trial (RCT) the least burdensome means to provide reasonable assurance that the subject device is safe and effective, or to establish substantial equivalence to a predicate, when used as indicated in the target population?"**

The main reason that the alternative question is wrong is that it conveniently dispenses with an important concept inherent in the regulation which states, ". . .the least burdensome appropriate means...." The concept of choosing an appropriate means is not fiivolous or cosmetic. What is appropriate is what is right. What is right when discussing medical devices is what is ethical in protecting the patient's rights, as agreed in the Declaration of Helsinki. The ethics of clinical trials comes into focus when we refer to them by their **generic name: human medical experiments.** Nobody wants to call them by this name, for fear of not having any patient in his right mind participating. (Naturally, anyone not in his right mind would be barred from taking part.) Creating a human medical experiment that is at the same time, ethical, unbiased, and capable of yielding

significant scientific data, is very difficult if not impossible. It is always difficult and extremely burdensome to try to find the right balance.

The crucial questions are: When are these experiments appropriate? When are these experiments necessary? If it is unnecessary, or inappropriate, then the question ofwhether it is least or most burdensome is purely academic. The decision concerning what sort of clinical study should be done to validate a new medical device should not be based primarily on financial considerations. The first consideration is what evidence is necessary to show the device is safe and effective, and if human subjects are involved, what is the most appropriate means for validating the device. The question of cost only becomes an issue if it appears to be an overwhelming one.

But even if cost is not the first question that should come to mind, it is still a consideration, so it is legitimate to ask, could doing an RCT be 'least burdensome'? As the FDA presents its case, the issue boils down to: at what point should one consider a Randomized Prospective Concurrent Clinical Trial (RCT). According to the FDA interpretation of the HIMA position, the manufacturers believe that only after all other sources are exhausted and shown to be insufficient should the last resort, the RCT be used. "FDA believes this approach would likely lead to the delay of market entry for many devices, an increase in the number of rounds of review required to assess each level of data and, therefore, more burden to both the industry and FDA." The FDA states that this may sometimes be such a long and laborious process that in the end the RCT, though difficult and extremely burdensome, may still be the ***least burdensome means. So they*** recommend that an RCT be considered much earlier in the process.

Both the assessment of the HIMA proposal, and the FDA response are mistaken.

1. The HIMA proposal does not state, as the FDA summarizes, that all avenues must be exhausted for each level of burden before the next is considered.

2. No sponsor would be so foolish as to waste their time and money making every submission at the lowest level possible because they would know that it would not have ". . . a reasonable likelihood of resulting in approval." Because it is so important to the sponsor to get FDA approval in a timely manner, he may actually submit with more valid scientific evidence than he thinks necessary in the expectation that the submission would have a have a greater likelihood of approval.

3. Finally, whatever level the sponsor might suggest, the FDA has a legal obligation to set the necessary level of proof. "Any clinical data, . . . specified in writing.. . shall be specified as result of a determination by the Secretary that such data are necessary.. . ."

For the reasons stated above, the assertion by the FDA that an RCT may be the least burdensome means, i.e. most cost efficient, for the sponsor is based on circumstances that are unlikely to occur.

On the issue of least burdensome one should also consider that, except where the control is no treatment, the use of a control device, as a practical matter, requires the ability to have power over the distribution of the control device sufficiently to allow its unhindered use and availability to the clinical investigators. If the company sponsoring the experiment manufactures and sells the control device then such distribution is readily achievable. Where, as is often the case with small companies, the company does not manufacture and sell a device that can be used as a control the company that does can influence the distribution and thus the availability of the control device. Usually this company is a competitor to the sponsoring company and thus has good reason to hinder such distribution since it would not want their competitor to sell a competing device, particularly if such a device was superior to theirs.

As a practical matter it would be easier for a company without a control device to gear up and manufacture such a device solely for the purpose of the clinical trial if they were forced to perform a concurrent control experiment rather than depend on the availability of the control device from a competitor. Such a trial would clearly be burdensome.

From a purely scientific viewpoint data from a concurrent control, random (RCT) experiment is the most efficient for a comparison with a control. Unfortunately, such an experiment is almost never appropriate for human clinical trials.

Consider the ethical problems of obtaining informed consent without coercion with an RCT. It is submitted that informed consent must be obtained from any individual 'in a clinical trial. To help understand the effect of this knowledge on the experiment consider:

Case 1 The treatment to be studied appears significantly superior in safety and efficacy to the control and the disease being treated greatly affects quality of life or is life threatening.

In such a case it is unethical for a physician to use the inferior treatment method. Failure to provide the best treatment for experimental purposes is in effect using that patient as an experimental animal and thus runs counter to our society's concept of the proper treatment of humans. Certainly the government, that exists only to serve and protect its people, should not attempt to force, or even allow, the use of humans as experimental animals under such circumstances.

Even where informed consent is obtained such consent would in effect be obtained by coercion since the patient would be given a choice of some chance to obtain the superior treatment if they signed, but no chance to obtain superior treatment if the did sign. Further the signing of an informed consent under such circumstances would introduce bias in the experiment.

Case 2 The treatment to be studied appears significantly superior in efficacy to the control, the disease being treated greatly affects quality of life or is life threatening, but there is significant risk associated with the treatment to be studied.

Here the informed consent involves an assessment of the risks and benefits. If this assessment can be quantified than the issue resolves to Case 1. If the assessment cannot be quantified then those patients who agree to be involved are different than those patients who do not and thus bias is introduced with the use of informed consent. The effect of this bias would then have to be compared (if possible) against the bias introduced by other methods in order to determine if RCT data is preferable.

Case 3 The treatment to be studied appears similar in efficacy to the control, the disease being treated greatly affects quality of life or is life threatening, but there is significant risk associated with the treatment to be studied.

This is equivalent to Case 1 where now since there is no advantage to the treatment to be studied but only risk, the control is the superior method.

Where the treatment to be studied appears similar in safety and efficacy to the control or the disease being treated does not greatly effects quality of life nor is life threatening. In this case, informed consent is not necessary and ifobtained would not introduce significant bias. This RCT is preferable.

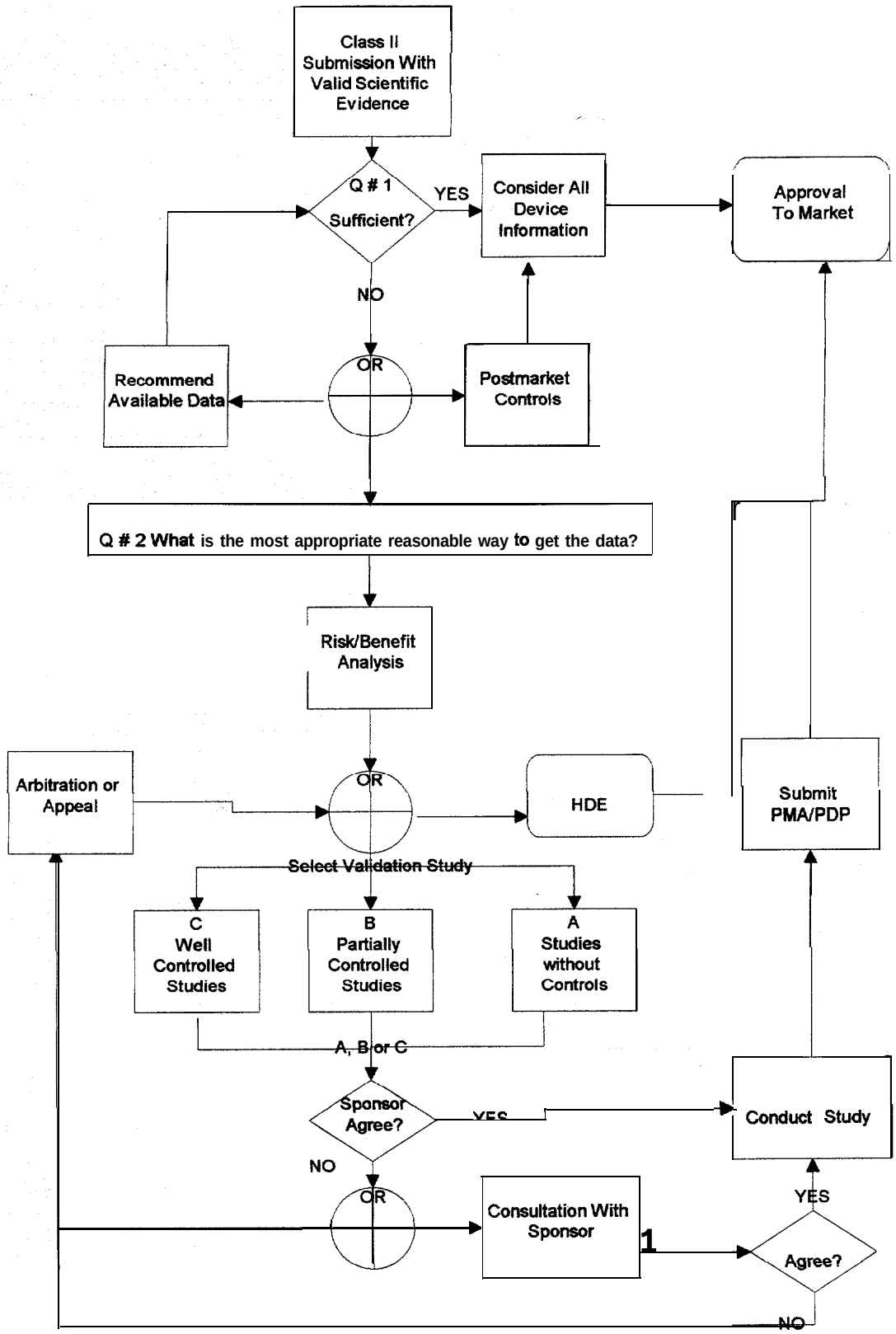
Thus the fundamental problem with the use of RCT for human clinical trials is that this method is limited to devices, which have a small impact on safety and efficacy. Whether such devices are even needed is an open question, but such devices normally would not require a clinical trial and thus the RCT is not of significant value in the clinical trials of medical devices.

The assumption that a randomized trial is the only acceptable method for evaluating a new medical device is not correct, as is the underlying assumption that the reason that the Medical Device Industry eschews the use of RCTs is that they are burdensome financially. In orthopedic device evaluation, RCTs are seldom used to validate implantable devices. The ultimate reason that as a manufacturer of implantable medical devices, Endotec refrains from RCTs in that they are seldom appropriate. Protecting the rights of patients as stipulated in the Declaration of Helsinki is the number one priority in weighing up the value of any clinical study used to validate medical devices, as enunciated in Basic Principle 5, "Concern for the interests of the subject must always prevail over the interests of science and society." An humane trial, even with some scientific uncertainty, is better than an inhumane trial.

To be required to do an inappropriate clinical trial is burdensome to the manufacturer whatever the cost may be. Furthermore, if an RCT is unnecessary, if the required data could be obtained by a clinical trial with no control, or a clinical trial using historical controls, to give but two examples of legitimate alternatives to an RCT, then an RCT is more burdensome to do, even if it is less burdensome financially.

In summation, an RCT is seldom necessary since other more appropriate methods usually are sufficient; unlikely to be least burdensome unless one considers it to be the only way, in which case it is least burdensome by default; and is almost never an appropriate method for a human medical experiment.

To reiterate, 'Medical Devices; Draft Guidance on Evidence Models for the Least Burdensome Means to Market; Availability' is a sound document that should be a credible basis for legislation on this matter, but only if the alternative to Question # 2, and all references to that alternative question are expunged from the document. It is an unnecessary and inappropriate question. If an RCT is the appropriate and necessary means for validating a particular new medical device, that decision will emerge from asking the global Question # 2, **'What is the most appropriate and reasonable way to obtain these data?", using the means mandated in the** law. The FDA shall, ". . . consider, in consultation with the applicant, the least burdensome appropriate means of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval." using the recommended standards for valid scientific evidence (studies and objective trials without matched controls, partially controlled studies, or well-controlled investigations) to determine what means are appropriate, what proof is necessary, and what would be the least burdensome method to show the safety and effectiveness of the medical device. See the attached flowchart for how the process might work in practice.



Created by John Pappas

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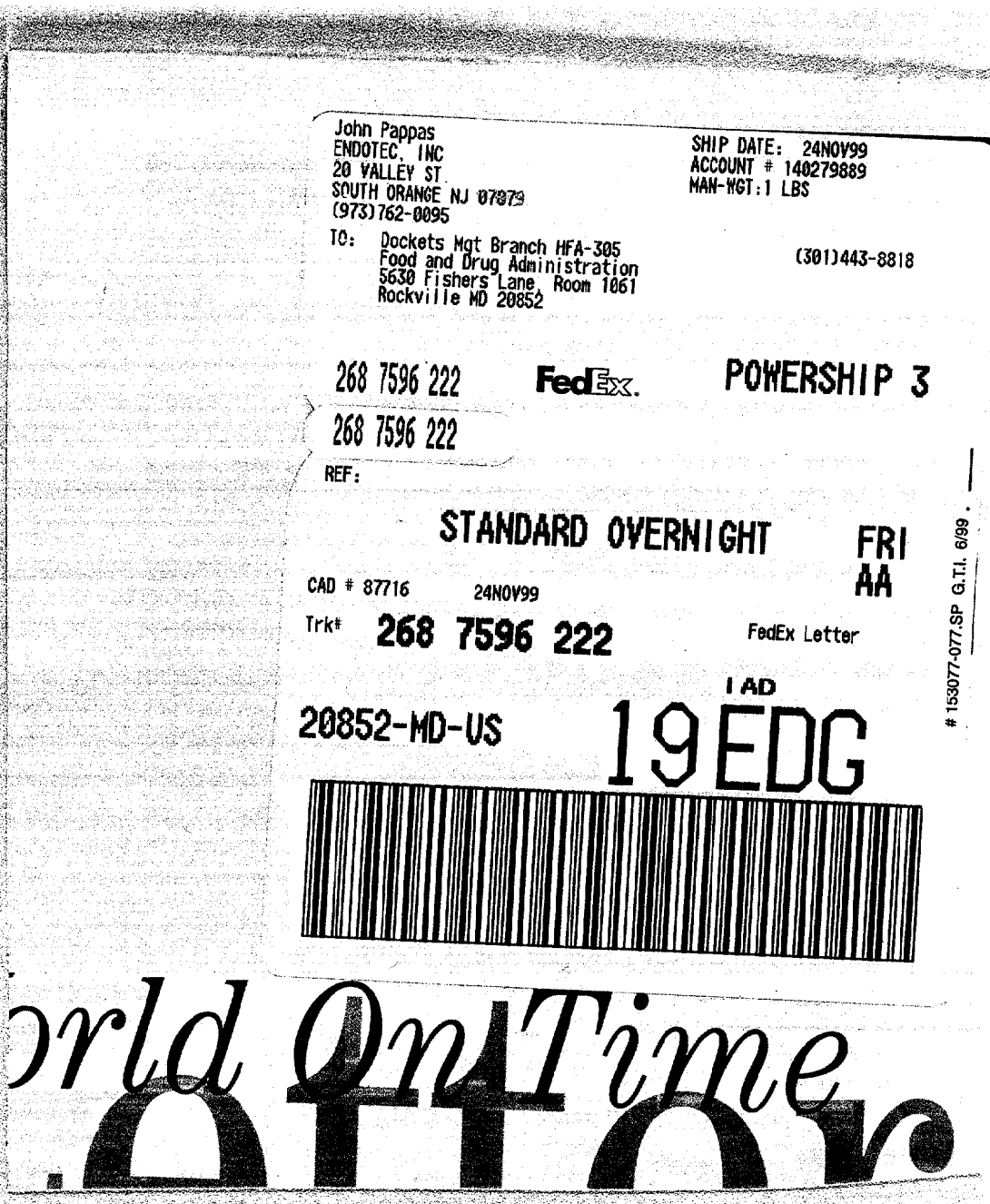

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